PATENT

IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

Applicants:	Zhang, et al.	) I hereby certify that this paper is
Serial No.:	To Be Determined	) being deposited with the United
Filed:	Herewith	) States Postal Service on **December**
For:	An Improved Method for the Production and Purification of Adenoviral Vectors	) **27, 2001**, in an envelope addressed
Continuation of:	09/556,570	) to the Commissioner for Patents,
Filed:	April 24, 2000	) Washington, D.C. 20231 utilizing
Art Unit:	Unknown	) the "Express Mail Post Office to
Examiner:	Unknown	) Addressee" service of the United
		) States Postal Service under Mailing
		) Label No. ET126944699US.
		)
		) Richard Zimmermann

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicant respectfully requests consideration of the following new claims. No fees beyond those enclosed are believed to be due. Should the Commissioner determine otherwise, he is authorized to charge Applicant's deposit account number 13-2855.

IN THE TITLE

Please amend the title as follows:

"Methods for Treating Patients with Adenoviral Vectors"

IN THE SPECIFICATION

Please amend the specification by deleting the text at lines 2 - 5 and replacing it with

the following:

The present application is a continuation of U.S. application serial number 09/556,570, filed April 24, 2000, which is a continuation of U.S. application serial number 08/975,519, filed November 20, 1997, which claims benefit of U.S. provisional application serial number 60/031,329, filed November 20, 1996. The entire text of the above-referenced disclosure is specifically incorporated by reference herein without disclaimer.

IN THE CLAIMS

Cancel claims 1-69. Add new claims 70-226 as follows:

70. A method of treating a patient with a therapeutic adenovirus composition, comprising:

a) obtaining a therapeutic adenovirus composition that has been prepared by a process that includes:

i) growing host cells in a media;

ii) providing nutrients to said host cells;

iii) infecting said host cells with an adenovirus;

iv) lysing said host cells to provide a lysate;

v) purifying adenovirus from said lysate to provide therapeutic adenovirus;

vi) formulating said therapeutic adenovirus to provide a therapeutic adenovirus composition;

b) administering said therapeutic adenovirus composition to a patient.

71. The method of claim 70, wherein the therapeutic adenovirus comprises 70% +/- 10% of the starting PFU.

72. The method of claim 70, wherein the therapeutic adenovirus comprises a substantially therapeutic adenovirus composition.

73. The method of claim 70, wherein the therapeutic adenovirus composition has a contaminating nucleic acid concentration of less than 0.8 ng/ml.

74. The method of claim 70, wherein the therapeutic adenovirus composition has a contaminating nucleic acid concentration of less than 0.2 ng/ml.

75. The method of claim 70, wherein the therapeutic adenovirus composition has an A_{260}/A_{280} ratio of between about 1.2 and 1.3.

76. The method of claim 70, wherein the therapeutic adenovirus composition has an A_{260}/A_{280} ratio of 1.27 +/- 0.03.

77. The method of claim 70, wherein the therapeutic adenovirus composition has a contaminating nucleic acid concentration of less than 0.8 ng/ml and an A_{260}/A_{280} ratio of between about 1.2 and 1.3.

78. The method of claim 70, wherein the therapeutic adenovirus composition has a BSA content below the detection level of a western blot assay.

79. The method of claim 70, wherein the media is serum-free.

80. The method of claim 70, wherein the host cells are grown in a bioreactor.

81. The method of claim 70, wherein the host cells are grown on microcarriers.

82. The method of claim 70, wherein the host cells are provided nutrients by perfusion.

83. The method of claim 70, wherein the host cells are provided nutrients by fed batch.

84. The method of claim 70, wherein the host cells are provided nutrients by automated roller bottle.

85. The method of claim 70, wherein said therapeutic adenovirus composition comprises an adenoviral vector encoding an exogenous gene construct.

86. The method of claim 85, wherein said exogenous gene construct is operatively linked to a promoter.

87. The method of claim 86, wherein said promoter is SV40 IE, RSV LTR, β-actin, CMV IE, adenovirus major late, polyoma F9-1, or tyrosinase.

88. The method of claim 85, wherein said exogenous gene construct encodes a therapeutic gene.

89. The method of claim 88, wherein said therapeutic gene encodes antisense *ras*, antisense *myc*, antisense *raf*, antisense *erb*, antisense *src*, antisense *fms*, antisense *jun*, antisense *trk*, antisense *ret*, antisense *gsp*, antisense *hst*, antisense *bcl*, antisense *abl*, Rb, CFTR, p16, p21, p27, p57, p73, C-CAM, APC, CTS-1, zac1, scFV *ras*, DCC, NF-1, NF-2, WT-1, MEN-1, MEN II, BRCA1, VHL, MMAC1, FCC, MCC, BRCA2, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, GM-CSF, G-CSF, thymidine kinase or p53.

90. The method of claim 88, wherein said therapeutic gene encodes p53.

91. The method of claim 70, wherein said therapeutic adenovirus composition is a replication-incompetent adenovirus.

92. The method of claim 91, wherein said replication-incompetent adenovirus composition is lacking at least a portion of the E1-region.

93. The method of claim 91, wherein said replication-incompetent adenovirus composition is lacking at least a portion of the E1A and/or E1B region.

94. The method of claim 70, wherein said host cells are capable of complementing replication.

95. The method of claim 70, wherein said host cells are 293 cells.

96. The method of claim 70, wherein said lysate is treated with a nuclease.

97. The method of claim 70, wherein said therapeutic adenovirus composition comprises a pharmaceutically acceptable buffer.

98. The method of claim 70, wherein said therapeutic adenovirus comprises a unit dose of between 10^3 and 10^{15} PFU/dose.

99. The method of claim 70, wherein said therapeutic adenovirus composition comprises a unit dose of between 10^{10} and 10^{14} PFU/dose.

100. The method of claim 70, wherein said patient is a cancer patient.

101. A method of treating a patient with a therapeutic adenovirus composition, comprising:

a) obtaining a therapeutic adenovirus composition that has been prepared by a process that includes:

i) growing host cells in a bioreactor or on a microcarrier;

ii) providing nutrients to said host cells ;

iii) infecting said host cells with an adenovirus;

iv) lysing said host cells to provide a lysate;

v) purifying adenovirus from said lysate to provide therapeutic adenovirus;

vi) formulating said therapeutic adenovirus to provide a therapeutic adenovirus composition;

b) administering said therapeutic adenovirus composition to a patient.

102. The method of claim 101, wherein the therapeutic adenovirus comprises 70% +/- 10% of the starting PFU.

103. The method of claim 101, wherein the therapeutic adenovirus comprises a substantially therapeutic adenovirus composition.

104. The method of claim 101, wherein the therapeutic adenovirus composition has a contaminating nucleic acid concentration of less than 0.8 ng/ml.

105. The method of claim 101, wherein the therapeutic adenovirus composition has a contaminating nucleic acid concentration of less than 0.2 ng/ml.

106. The method of claim 101, wherein the therapeutic adenovirus composition has an A_{260}/A_{280} ratio of between about 1.2 and 1.3.

107. The method of claim 101, wherein the therapeutic adenovirus composition has an A_{260}/A_{280} ratio of 1.27 +/- 0.03.

108. The method of claim 101, wherein the therapeutic adenovirus composition has a contaminating nucleic acid concentration of less than 0.8 ng/ml and an A_{260}/A_{280} ratio of between about 1.2 and 1.3.

109. The method of claim 101, wherein the therapeutic adenovirus composition has a BSA content below the detection level of a western blot assay.

110. The method of claim 101, wherein the media is serum-free.

111. The method of claim 101, wherein the host cells are grown in a bioreactor.

112. The method of claim 101, wherein the host cells are grown on microcarriers.

113. The method of claim 101, wherein the host cells are provided nutrients by perfusion.

114. The method of claim 101, wherein the host cells are provided nutrients by fed batch.

115. The method of claim 101, wherein the host cells are provided nutrients by automated roller bottle.

116. The method of claim 101, wherein said therapeutic adenovirus composition comprises an adenoviral vector encoding an exogenous gene construct.

117. The method of claim 116, wherein said exogenous gene construct is operatively linked to a promoter.

118. The method of claim 117, wherein said promoter is SV40 IE, RSV LTR, β-actin, CMV IE, adenovirus major late, polyoma F9-1, or tyrosinase.

119. The method of claim 116, wherein said exogenous gene construct encodes a therapeutic gene.

120. The method of claim 119, wherein said therapeutic gene encodes antisense *ras*, antisense *myc*, antisense *raf*, antisense *erb*, antisense *src*, antisense *fms*, antisense *jun*, antisense *trk*, antisense *ret*, antisense *gsp*, antisense *hst*, antisense *bcl*, antisense *abl*, Rb, CFTR, p16, p21, p27, p57, p73, C-CAM, APC, CTS-1, zac1, scFV *ras*, DCC, NF-1, NF-2, WT-1, MEN-1, MEN II, BRCA1, VHL, MMAC1, FCC, MCC, BRCA2, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, GM-CSF, G-CSF, thymidine kinase or p53.

121. The method of claim 119, wherein said therapeutic gene encodes p53.

122. The method of claim 101, wherein said therapeutic adenovirus composition is a replication-incompetent adenovirus.

123. The method of claim 122, wherein said replication-incompetent adenovirus composition is lacking at least a portion of the E1-region.

124. The method of claim 122, wherein the replication-incompetent adenovirus composition is lacking at least a portion of the E1A and/or E1B region.

125. The method of claim 101, wherein said host cells are capable of complementing replication.

126. The method of claim 101, wherein said host cells are 293 cells.

127. The method of claim 101, wherein said lysate is treated with a nuclease.

128. The method of claim 101, wherein said therapeutic adenovirus composition comprises a pharmaceutically acceptable buffer.

129. The method of claim 101, wherein said therapeutic adenovirus composition comprises a unit dose of between 10^3 and 10^{15} PFU/dose.

130. The method of claim 101, wherein said therapeutic adenovirus composition comprises a unit dose of between 10^{10} and 10^{-4} PFU/dose.

131. The method of claim 101, wherein said patient is a cancer patient.

132. A method of treating a patient with a therapeutic adenovirus composition, comprising:

a) obtaining a therapeutic adenovirus composition that has been prepared by a process that includes:

i) growing host cells in a media;

ii) providing nutrients to said host cells by perfusion or through a fed batch or roller bottle process;

iii) infecting said host cells with an adenovirus;

iv) lysing said host cells to provide a lysate;

v) purifying adenovirus from said lysate to provide therapeutic adenovirus;

vi) formulating said therapeutic adenovirus to provide a therapeutic adenovirus composition;

b) administering said therapeutic adenovirus composition to a patient.

133. The method of claim 132, wherein the therapeutic adenovirus composition comprises 70% +/- 10% of the starting PFU.

134. The method of claim 132, wherein the therapeutic adenovirus composition comprises a substantially therapeutic adenovirus composition.

135. The method of claim 132, wherein the therapeutic adenovirus composition has a contaminating nucleic acid concentration of less than 0.8 ng/ml.

136. The method of claim 132, wherein the therapeutic adenovirus composition has a contaminating nucleic acid concentration of less than 0.2 ng/ml.

137. The method of claim 132, wherein the therapeutic adenovirus composition has an A_{260}/A_{280} ratio of between about 1.2 and 1.3.

138. The method of claim 132, wherein the therapeutic adenovirus composition has an A_{260}/A_{280} ratio of 1.27 +/- 0.03.

139. The method of claim 132, wherein the therapeutic adenovirus composition has a contaminating nucleic acid concentration of less than 0.8 ng/ml and an A_{260}/A_{280} ratio of between about 1.2 and 1.3.

140. The method of claim 132, wherein the therapeutic adenovirus composition has a BSA content below the detection level of a western blot assay.

141. The method of claim 132, wherein the media is serum-free.

142. The method of claim 132, wherein the host cells are grown in a bioreactor.

143. The method of claim 132, wherein the host cells are grown on microcarriers.

144. The method of claim 132, wherein the host cells are provided nutrients by perfusion.

145. The method of claim 132, wherein the host cells are provided nutrients by fed batch.

146. The method of claim 132, wherein the host cells are provided nutrients by automated roller bottle.

147. The method of claim 132, wherein said therapeutic adenovirus composition comprises an adenoviral vector encoding an exogenous gene construct.

148. The method of claim 147, wherein said exogenous gene construct is operatively linked to a promoter.

149. The method of claim 150, wherein said promoter is SV40 IE, RSV LTR, β-actin, CMV IE, adenovirus major late, polyoma F9-1, or tyrosinase.

150. The method of claim 149, wherein said exogenous gene construct encodes a therapeutic gene.

151. The method of claim 150, wherein said therapeutic gene encodes antisense *ras*, antisense *myc*, antisense *raf*, antisense *erb*, antisense *src*, antisense *fms*, antisense *jun*, antisense *trk*, antisense *ret*, antisense *gsp*, antisense *hst*, antisense *bcl*, antisense *abl*, Rb, CFTR, p16, p21, p27, p57, p73, C-CAM, APC, CTS-1, zac1, scFV *ras*, DCC, NF-1, NF-2, WT-1, MEN-1, MEN II, BRCA1, VHL, MMAC1, FCC, MCC, BRCA2, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, GM-CSF, G-CSF, thymidine kinase or p53.

152. The method of claim 150, wherein said therapeutic gene encodes p53.

153. The method of claim 132, wherein said therapeutic adenovirus composition is a replication-incompetent adenovirus.

154. The method of claim 153, wherein said replication-incompetent adenovirus composition is lacking at least a portion of the E1-region.

155. The method of claim 153, wherein the replication-incompetent adenovirus composition is lacking at least a portion of the E1A and/or E1B region.

156. The method of claim 132, wherein said host cells are capable of complementing replication.

157. The method of claim 132, wherein said host cells are 293 cells.

158. The method of claim 132, wherein said lysate is treated with a nuclease.

159. The method of claim 132, wherein said therapeutic adenovirus composition comprises is pharmaceutically acceptable buffer.

160. The method of claim 132, wherein said therapeutic adenovirus composition comprises a unit dose of between 10^3 and 10^{15} PFU/dose.

161. The method of claim 132, wherein said therapeutic adenoviral composition comprises a unit dose of between 10^{10} and 10^{14} PFU/dose.

162. The method of claim 132, wherein said patient is a cancer patient.

163. A method of treating a patient with a therapeutic adenovirus composition, comprising:

a) obtaining a therapeutic adenovirus composition that has been prepared by a process that includes:

i) growing host cells in a media;

ii) providing nutrients to said host cells;

iii) infecting said host cells with an adenovirus;

iv) lysing said host cells by a lysis method other than freeze-thaw to provide a cell lysate;

v) purifying adenovirus from said cell lysate to provide therapeutic adenovirus;

vi) formulating said therapeutic adenovirus to provide a therapeutic adenovirus composition;

b) administering said therapeutic adenovirus composition to a patient.

164. The method of claim 163, wherein the therapeutic adenovirus composition comprises 70% +/- 10% of the starting PFU.

165. The method of claim 163, wherein the therapeutic adenovirus composition comprises a substantially therapeutic adenovirus composition.

166. The method of claim 163, wherein the therapeutic adenovirus composition has a contaminating nucleic acid concentration of less than 0.8 ng/ml.

167. The method of claim 163, wherein the therapeutic adenovirus composition has a contaminating nucleic acid concentration of less than 0.2 ng/ml.

168. The method of claim 163, wherein the therapeutic adenovirus composition has an A_{260}/A_{280} ratio of between about 1.2 and 1.3.

169. The method of claim 163, wherein the therapeutic adenovirus composition has an A_{260}/A_{280} ratio of 1.27 +/- 0.03.

170. The method of claim 163, wherein the therapeutic adenovirus composition has a contaminating nucleic acid concentration of less than 0.8 ng/ml and an A_{260}/A_{280} ratio of between about 1.2 and 1.3.

171. The method of claim 163, wherein the therapeutic adenovirus composition has a BSA content below the detection level of a western blot assay.

172. The method of claim 163, wherein the media is serum-free.

173. The method of claim 163, wherein the host cells are grown in a bioreactor.

174. The method of claim 163, wherein the host cells are grown on microcarriers.

175. The method of claim 163, wherein the host cells are provided nutrients by perfusion.

176. The method of claim 163, wherein the host cells are provided nutrients by fed batch.

177. The method of claim 163, wherein the host cells are provided nutrients by automated roller bottle.

178. The method of claim 163, wherein said therapeutic adenovirus composition comprises an adenoviral vector encoding an exogenous gene construct.

179. The method of claim 178, wherein said exogenous gene construct is operatively linked to a promoter.

180. The method of claim 179, wherein said promoter is SV40 IE, RSV LTR, β-actin, CMV IE, adenovirus major late, polyoma F9-1, or tyrosinase.

181. The method of claim 178, wherein said exogenous gene construct encodes a therapeutic gene.

182. The method of claim 181, wherein said therapeutic gene encodes antisense *ras*, antisense *myc*, antisense *raf*, antisense *erb*, antisense *src*, antisense *fms*, antisense *jun*, antisense *trk*, antisense *ret*, antisense *gsp*, antisense *hst*, antisense *bcl*, antisense *abl*, Rb, CFTR, p16, p21, p27, p57, p73, C-CAM, APC, CTS-1, zac1, scFV *ras*, DCC, NF-1, NF-2, WT-1, MEN-1, MEN II, BRCA1, VHL, MMAC1, FCC, MCC, BRCA2, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, GM-CSF, G-CSF, thymidine kinase or p53.

183. The method of claim 181, wherein said therapeutic gene encodes p53.

184. The method of claim 163, wherein said therapeutic adenovirus composition is a replication-incompetent adenovirus.

185. The method of claim 184, wherein said replication-incompetent adenovirus composition is lacking at least a portion of the E1-region.

186. The method of claim 184, wherein the replication-incompetent adenovirus composition is lacking at least a portion of the E1A and/or E1B region.

187. The method of claim 163, wherein said host cells are capable of complementing replication.

188. The method of claim 163, wherein said host cells are 293 cells.

189. The method of claim 163, wherein said lysate is treated with a nuclease.

190. The method of claim 163, wherein said therapeutic adenovirus composition comprises is pharmaceutically acceptable buffer.

191. The method of claim 163, wherein said therapeutic adenovirus composition comprises a unit dose of between 10^3 and 10^{15} PFU/dose.

192. The method of claim 163, wherein said therapeutic adenovirus composition comprises a unit dose of between 10^{10} and 10^{14} PFU/dose.

193. The method of claim 163, wherein said patient is a cancer patient.

194. A method of treating a patient with a therapeutic adenovirus composition, comprising:

a) obtaining a therapeutic adenovirus composition that has been prepared by a process that includes:

i) growing host cells in a media;

ii) providing nutrients to said host cells;

iii) infecting said host cells with an adenovirus;

iv) lysing said host cells to provide a lysate;

v) purifying adenovirus from said lysate by a method that includes at least one chromatography step, without the use of cesium chloride

density gradient centrifugation capable of providing therapeutic adenovirus;

vi) formulating said therapeutic adenovirus to provide a therapeutic adenovirus composition;

b) administering said therapeutic adenovirus composition to a patient.

195. The method of claim 194, wherein the therapeutic adenovirus composition comprises 70% +/- 10% of the starting PFU.

196. The method of claim 194, wherein the therapeutic adenovirus composition comprises a substantially therapeutic adenovirus composition.

197. The method of claim 194, wherein the therapeutic adenovirus composition has a contaminating nucleic acid concentration of less than 0.8 ng/ml.

198. The method of claim 194, wherein the therapeutic adenovirus composition has a contaminating nucleic acid concentration of less than 0.2 ng/ml.

199. The method of claim 194, wherein the therapeutic adenovirus composition has an A_{260}/A_{280} ratio of between about 1.2 and 1.3.

200. The method of claim 194, wherein the therapeutic adenovirus composition has an A_{260}/A_{280} ratio of 1.27 +/- 0.03.

201. The method of claim 194, wherein the therapeutic adenovirus composition has a contaminating nucleic acid concentration of less than 0.8 ng/ml and an A_{269}/A_{280} ratio of between about 1.2 and 1.3.

202. The method of claim 194, wherein the therapeutic adenovirus composition has a BSA content below the detection level of a western blot assay.

203. The method of claim 194, wherein the media is serum-free.

204. The method of claim 194, wherein the host cells are grown in a bioreactor.

205. The method of claim 194, wherein the host cells are grown on microcarriers.

206. The method of claim 194, wherein the host cells are provided nutrients by perfusion.

207. The method of claim 194, wherein the host cells are provided nutrients by fed batch.

208. The method of claim 194, wherein the host cells are provided nutrients by automated roller bottle.

209. The method of claim 194, wherein said therapeutic adenovirus composition comprises an adenoviral vector encoding an exogenous gene construct.

210. The method of claim 209, wherein said exogenous gene construct is operatively linked to a promoter.

211. The method of claim 210, wherein said promoter is SV40 IE, RSV LTR, β-actin, CMV IE, adenovirus major late, polyoma F9-1, or tyrosinase.

212. The method of claim 209, wherein said exogenous gene construct encodes a therapeutic gene.

213. The method of claim 212, wherein said therapeutic gene encodes antisense *ras*, antisense *myc*, antisense *raf*, antisense *erb*, antisense *src*, antisense *fms*, antisense *jun*, antisense *trk*, antisense *ret*, antisense *gsp*, antisense *hst*, antisense *bcl*, antisense *abl*, Rb, CFTR, p16, p21, p27, p57, p73, C-CAM, APC, CTS-1, zac1, scFV *ras*, DCC, NF-1, NF-2, WT-1, MEN-1, MEN II, BRCA1, VHL, MMAC1, FCC, MCC, BRCA2, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, GM-CSF, G-CSF, thymidine kinase or p53.

214. The method of claim 212, wherein said therapeutic gene encodes p53.

215. The method of claim 194, wherein said therapeutic adenovirus composition is a replication-incompetent adenovirus.

216. The method of claim 215, wherein said replication-incompetent adenovirus composition is lacking at least a portion of the E1-region.

217. The method of claim 215, wherein the replication-incompetent adenovirus composition is lacking at least a portion of the E1A and/or E1B region.

218. The method of claim 194, wherein said host cells are capable of complementing replication.

219. The method of claim 194, wherein said host cells are 293 cells.

220. The method of claim 194, wherein said lysate is treated with a nuclease.

221. The method of claim 194, wherein said therapeutic adenovirus composition comprises is pharmaceutically acceptable buffer.

222. The method of claim 194, wherein said therapeutic adenovirus composition comprises a unit dose of between 10^{3} and 10^{15} PFU/dose.

223. The method of claim 194, wherein said therapeutic adenovirus commission comprises a unit dose of between 10^{10} and 10^{14} PFU/dose.

224. The method of claim 194, wherein said patient is a cancer patient.

225. The method of claim 194, wherein the chromatography step is a single chromatography step.

226. The method of claim 230, wherein said single chromatography step is anion exchange chromatography.

REMARKS

New claims 70-226 have been added and are considered pending. The Examiner is respectfully requested to consider these claims. Support for claims 70, 82-84, 101, 113-115, 132, 144-146, 163, 175-177, 194, 206-208, 225 and 226 is found throughout the specification, particularly at the following locations: page 11, line 12 through page 109, line 20. Support for claims 71, 102, 133, 164 and 195 is found throughout the specification, particularly at the following locations: page 12, line 5 and page 99, line 28 through page 100, line 8. Support for claims 72, 103, 134, 165 and 196 is found throughout the specification, particularly at the following locations: page 64 lines 13-18. Support for claims 73, 74, 101, 105, 135, 136, 166, 167, 197 and 198 is found throughout the specification, particularly at the following locations: page 92, lines 10-20, Table 10. Support for claims 75-77, 106-108, 137-139, 168-170, and 199-201 is found throughout the specification, particularly at the following locations: page 91, lines 1-13. Support for claims 78, 109, 140, 171 and 202 is found throughout the specification, particularly at the following locations: pages 38-41, 43-57, 87, 92, and 93. Support for claims 79, 110, 141, 172 and 203 is found throughout the specification, particularly at the following locations: page 15, lines 16-28, page 16, lines 17-29, page 27, lines 25 and 30, page 28, lines 1-30, page 100, lines 18 through page 105, line 28 and Tables 12 and 13. Support for claims 80, 111, 142, 173 and 204 is found throughout the specification, particularly at the following locations: page 17, line 24 through page 18, line 18. Support for claims 81, 112, 143, 174 and 205 is found throughout the specification, particularly at the following locations: page 22, line 8, through page 23, line 11. Support for claims 85-100, 116-131, 147-162, 178-193, and 209-224 is found throughout the specification, particularly at the following locations: page 72, line 11 through page 75, line 18.

It is submitted that each of claims 70-226 should now be indicated to be allowable. Should the Examiner have any questions of form or substance, he or she is invited to contact the undersigned attorney at the number listed below.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN

By: _____
Jeffrey S. Sharp
Registration No. 31,879
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6402
(312) 474-6300

Date: December 27, 2001